Applicants thank Examiner Ewoldt and Primary Examiner Nolan for the telephonic interview conducted on July 18, 2001. Specific points requested to be further described in Applicant's response are detailed below.

REMARKS

Claims 1-7, 18 and 19 are pending in the application. A copy of the claims as currently pending is attached hereto. Each of the rejections of the claims shall be addressed below. Reconsideration and withdrawal of the rejections to Claims 1-7, 18 and 19 in view of the discussion in the telephonic interview and the following remarks is respectfully requested.

1. Rejections based on U.S. Patent No. 5,997,863.

A. Claims 1-7, 18 and 19 were rejected under 35 USC § 102(e) or (f) over U.S. Patent No. 5,997,863. As discussed in the telephone interview, Applicants have submitted herewith a Declaration of Inventor under 37 CFR §1.132 which states that the above referenced application was made by the inventors of the instant application. Therefore, the invention claimed in the instant application was not made "by another" and this rejection should be withdrawn.

B. It was stated that Claims 1-7, 18 and 19 would be rejected under 35 USC § 103(a) over U.S. Patent No. 5,997,863 absent a showing that U.S. Patent No. 5,997,863 does not qualify as prior art under 35 USC § 102(f) or (g). As discussed in the telephone interview, Applicants have submitted herewith a Declaration of Assignee under 37 CFR §1.132 which states that the above referenced application was commonly owned with U.S. Patent No. 5,997,863 at the time the invention claimed in the above referenced application was made. Accordingly, U.S. Patent No. 5,997,863 does not qualify as prior art under 35 USC § 102(f) or (g) and thus a rejection of the claims of the instant application under 35 USC § 103(a) is precluded.

C. Claims 1-7, 18 and 19 were also rejected under the judicially created doctrine of obviousness type double patenting over claims 1–10 of U.S. Patent No. 5,997,863. Applicants have submitted herewith a terminal disclaimer which complies with the requirements of 37 CFR §1.321, and §3.73(b). Accordingly, this rejection should be withdrawn.

2. Request for Reconsideration of Declaration under 37 CFR §1.131.

Applicants respectfully request reconsideration of the Declaration under 37 CFR §1.131 (hereafter "the Rule 1.131 Declaration") which was submitted on January 5, 1999 together with a petition to waive the requirement of 37 CFR §1.131. The petition was granted in the Decision on Petition mailed June 3, 1999.

Applicants submit that for the reasons detailed below, the claims of the above referenced application are entitled to the filing date of September 29, 1995 which is the filing date of Provisional Patent Application No. 60/004,622 to which provisional application the instant application claims priority. Applicants further submit that for the reasons detailed below, the Rule 1.131 Declaration is sufficient to establish that the claimed invention was conceived and reduced to practice prior to the publication date of each of the cited articles which were published less than one year prior to the effective filing date of the instant application. Accordingly the following references should be removed from consideration during examination of this application: the primary references Hoogewerf et al. (1995) *J. Biol. Chem.*, **270**:3268 and Gilat et al. (1995) *J. Exp. Med.*, **181**:1929, and all three of the secondary references Nash et al. (1995) *J. of Pharm. and Exp. Ther.*, **274**:1436, Lider et al. (1995) *Proc. Natl. Acad. Sci., USA*, **92**:5037, and Gilat et al. (1994) *J. Immunol.*, **153**:4899, published December 31, 1994.

The claimed invention is a method to decrease localized inflammatory responses arising from an ischemia/reperfusion injury in a tissue of a patient comprising intravascularly administering to said patient heparinase enzyme in an effective amount sufficient to decrease neutrophil transmigration through activated endothelium and basement membrane of said vasculature which decreases said localized inflammatory response arising from an ischemia/reperfusion injury.

The Rule 1.131 Declaration presents the results obtained using an *in vitro* assay which is an accepted model system for the analysis of conditions affecting neutrophil transmigration across activated endothelium and basement membrane of the vasculature. A description of this model system and the results obtained when assessing the affect of heparinase III on neutrophil transmigration are presented in the Rule 1.131 Declaration, and this identical information was also were included in Example 4 (pages 26-29) of the provisional application to which the instant application claims priority, and in Example 5 (pages 31-33) of the instant application.

The protocol for the model system described in the Rule 1.131 Declaration is a modification of accepted model systems for assessment of agents which alter neutrophil transmigration to subendothelial tissues, which transmigration is the first step in a inflammatory response, (see Cotran et al., page 47 (cited by the Examiner in Paper No. 19), and Huber et al., 1991, Science, 254:99-102, see the legend for Figure 1 which provides the description of the model system (previously provided in Applicants' Response which was hand delivered on May 23, 2000).

The Rule 1.131 Declaration and its supporting documents demonstrate that, as measured by this *in vitro* assay, heparinase III is useful to decrease neutrophil transmigration through activated endothelium and basement membrane of the vasculature. The link between a decrease in neutrophil transmigration across the endothelium and basement membrane of the vasculature and a decrease in the localized inflammatory response is further detailed below.

Localized inflammation has long been established to result from leukocyte transmigration across the vascular endothelium and basement membrane to the site of tissue injury. The first type of leukocytes to transmigrate are neutrophils, (see, for example, Cotran et al., Huber et al., cited above, and Lefer and Lefer, 1993, Ann. Rev. Pharmacol. Toxicol, 33:71-90). A copy of each of publication is included herewith for the Examiner's convenience.

As described in Cotran et al., the accumulation of leukocytes is the most important feature of the inflammatory reaction, and in most types of acute inflammation, neutrophils predominate first (see page 46, second column, final paragraph). The sequence of leukocyte events during inflammation are stated on page 45 of Cotran et al. to be divided into (1) margination,(2) adhesion, (3) emigration toward a chemotactic stimulus ("transmigration"), (4) phagocytosis and intracellular degradation, and (5) extracellular release of leukocyte products. As stated by Cotran et al. on pages 46-47, leukocyte adhesion and subsequent emigration are key steps in inflammation, and the presence of cytokines is required for such adhesion and transmigration by neutrophils. Disruption of these steps serves to decrease the localized inflammatory response.

As described in Huber et al., binding of neutrophils to activated endothelium initiates an orchestrated series of events in which neutrophils bind to the surface of the endothelium and then penetrate the vessel wall and proceed into the interstitium (see page 99, 1st paragraph). After

presenting evidence that heparin bound chemotactic factors induce neutrophil adherence and transmigration in the model system, Huber et al., concludes by noting that the development of inhibitors of the chemotactic factors could lead to the development of anti-inflammatory therapies (see page 101, third column, final paragraph).

As described in Lefer et al., ischemia leads to hypoxia which, if severe enough, can lead to reduced energy metabolism and then to a slow but significant degree of tissue injury and necrosis, which tissue injury is further enhanced and accelerated by reperfusion (see page 75, first paragraph). Reperfusion, through a series of alterations of the vascular endothelium, leads to polymorphonuclear ("PMN") leukocyte (i.e. neutrophil) adherence which leukocytes transmigrate through the vascular endothelium (by diapedesis) and localize to compromised cells where they release a host of pro-inflammatory mediators which in turn promote cell injury (see pages 75-76, bridging paragraph). Lefer states that an agent which can inhibit neutrophils or their mediators would preserve endothelial function and thus reduce inflammation that would otherwise arise from ischemia/reperfusion (see, page 76, final paragraph and pages 80-81 (specifically page 81, second paragraph).

Applicants conceived of the invention that heparinase would be useful to disrupt the steps which lead to localized inflammatory response, and reduced this invention to practice using the accepted model system for neutrophil transmigration described in the Rule 1.131 Declaration. Applicants further validated the results presented in the Rule 1.131 Declaration by analyzing additional heparinase enzymes with this model system (see Example 4 of the provisional application and Examples 5 and 6 of the instant application). In addition, Applicants conducted *in vivo* experiments to further validate their discovery that intravascular administration of heparinase enzyme will decrease neutrophil adhesion and transmigration through activated endothelium and basement membrane of the vasculature subsequent to an ischemic event thereby decreasing the localized inflammatory response which would have otherwise arisen from an ischemia/reperfusion injury to tissue. (see Example 7, pages 35-39 of the specification). Specifically, in Example 7, intravital video microscopy was used to quantitate neutrophil movement through the vasculature after an ischemic event in rats, and neutrophil movement in untreated rats was compared with that in heparinase treated rats. As described in the specification, pages 38, line 28 through 39, line 8 and shown in Figures 12-14, in untreated rats

the number of leukocytes which adhered to the endothelial walls of the vasculature and extravasated progressively increased during reperfusion, but in heparinase treated rats no significant difference was observed for either leukocyte adhesion or extravasation when compared to control animals which had not been subject to an ischemic event.

In view of the foregoing discussion, Applicants' respectfully submit that the Rule 1.131 Declaration demonstrates that Applicants conceived of, and reduced to practice, the claimed invention prior to the publication of any of the above listed references. Accordingly, Applicants respectfully request that the above listed references be withdrawn from consideration of the allowability of the claimed invention.

3. The claims are patentable under 35 USC § 103 in view of the cited art.

Claims 1-7, 18 and 19 remain rejected under 35 USC §103(a) as being unpatentable in view of a combination of nine references. Specifically, Hoogewerf et al, Gilat et al. (X) (*J. Exp. Med.* (1995) **181**:1929), Vlodavsky et al., U.S. Patent No. 5,169,722, U.S. Patent No. 5,362,641 and U.S. Patent No. 5,567,417 in view of the teachings of Nash et al., Lider et al., and Gilat et al. (AA) (*J. Immunol.* (1994) **153**:4899). This rejection is respectfully traversed.

Notwithstanding Applicants request for reconsideration of the Declaration under 37 CFR §1.131 above, which if accepted upon reconsideration would result in the removal of this rejection due to a withdrawal of all of the secondary references cited, Applicants respectfully submit that there is no motivation in the cited art to combine the cited references in order to decrease localized inflammatory responses arising from an ischemia/reperfusion injury in a tissue of a patient by intravascularly administering to said patient heparinase enzyme in an effective amount sufficient to decrease neutrophil transmigration through activated endothelium and basement membrane of said vasculature which decreases said localized inflammatory response arising from an ischemia/reperfusion injury, as is claimed in the instant application.

As noted by the Examiner, each of Hoogewerf et al, Gilat et al. (X), Vlodavsky et al. and the '722 patent are cited as they teach heparinase enzymes obtained from different sources but none of these articles teach the use of these heparinase enzymes to decrease an inflammatory response, nor do any of these articles teach that a heparinase enzyme decreases neutrophil transmigration through activated vascular endothelium and basement membrane.

The '641 patent and the '417 patent were stated to "disclose but not exemplify administration of heparinases to treat localized inflammatory responses in a variety of diseases." Applicants object to this characterization of the '641 and '417 patents as it is incorrect.

The '641 patent teaches in col. 4, line 38 through col. 5, line 6, that fibroblast growth factor (FGF) appears to play a significant role in the mechanisms involved in wound healing, specifically by way of its promotion of angiogenesis. FGF is further described to be bound in the extracellular matrix to heparan sulfate, and it is suggested that addition of heparanase may provide an effective method to mobilize and activate FGF. The '641 patent goes on to suggest several pathological conditions that may benefit from the neovascularization promoted by FGF, including cardiac, cerebral and peripheral ischemic diseases (col. 4, line 66 through col. 5, line 6). Nowhere in the '641 patent or in any other cited publication is there a suggestion that a method for the promotion of neovascularization would also result in a decrease in localized inflammatory response arising from an ischemia/reperfusion injury.

The '417 patent teaches in col. 1, line 47 through col. 2, line 4, that a number of diseases, including inflammatory eye disease, are dominated by abnormal neovascularization, and further teaches in col. 4 and 5 that heparinases directly inhibit neovascularization. However, nowhere in the '417 patent is there a suggestion that a method for inhibiting neovascularization would also result in a decrease in localized inflammatory response arising from an ischemia/reperfusion injury.

Nash et al. is relied upon for teaching that angiogenesis is required for the progression of chronic inflammation. Nash et al., however, provides no suggestion that angiogenesis is involved in a localized inflammatory response arising from an ischemia reperfusion injury.

Lider et al. is relied upon for teaching that heparinase inhibits secretion of TNFα by activated T cells. Lider et al. teaches that TNFα is secreted by T cell as one step of a delayed-type hypersensitivity response. There is no teaching or suggestion, however, that T cells are activated to produce TNFα due to an ischemia/reperfusion injury.

Gilat et al. (1994) is relied upon as teaching that "heparinases degrade heparin from the ECM which leads to the release of cytokines which leads to leukocytes becoming mobile" and references page 4909 for this teaching. Applicants respectfully point out there is no page 4909 in this publication. A careful reading of Gilat et al. demonstrates that nowhere in Gilat et al. is

there a teaching or suggestion that heparinases would be useful to decrease the localized inflammatory response arising from an ischemia/reperfusion injury.

Based on the foregoing remarks and the discussion in the interview, the Examiner is respectfully requested to reconsider and withdraw this rejection of claims 1-7, 18 and 19.

Summary

Reconsideration of the application, in view of the telephonic interview conducted on July 18, 2001 and the foregoing remarks, is respectfully requested. The application should be in condition for allowance, and such action is respectfully requested. If the Examiner believes that a telephone conversation would expedite prosecution in this Application, the Examiner is invited to telephone the undersigned at (617) 526-6460.

Respectfully submitted,
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Dated: August 9, 2001

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